

THE CHEMISTRY OF VICINAL TRICARBONYL COMPOUNDS:  
CONDENSATION REACTIONS OF ETHYL 3-PHENYL-2,3-DIOXOPROPANOATE

by

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## INTRODUCTION

The reactions of monofunctional organic compounds have been studied extensively. Reactions of poly-functional compounds are less well known, particularly the interaction of neighboring groups and their effects on a normal reaction of a single group. The study of poly-functional compounds is particularly important because of the great number of such compounds which exist in natural products.

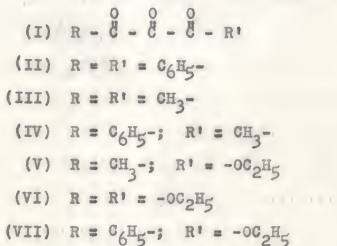
Vicinal tricarbonyl compounds I, (Table 1), comprise a group of chemically related substances containing three adjacent carbonyl groups. The adjacent groups may be ketone groups or a combination of aldehyde, ketone, or ester groups linked so that three vicinal carbonyl groups exist in the resultant molecule. Such compounds provide possibilities for interesting combinations of carbonyl groups and the elucidation of which group is susceptible to specific reagents might provide information concerning the structure of the compound and the mechanisms of its reactions.

A possibility for practical use of this group of compounds is demonstrated in the use of ninhydrin, or triketohydrindene hydrate, as a test reagent in biochemical determinations. Abderhalden and Schmidt (1) reported the use of triketohydrindene hydrate as a reagent in the quantitative determination of amino acids in the tissues and issues of the human body.

The first synthesis of a tricarbonyl compound was achieved by de Neufville and von Peckmann (12) who prepared 1,3-diphenyl

propanetrione-1,2,3 (II) in 1891. Sachs and Barschall (13) prepared pentanetrione-2,3,4 (III) in 1901 and the synthesis of 1-phenylbutanetrione-1,2,3 (IV) was first reported by Sachs and Rohmer (15) in 1902. The mixed ester diketone type molecule, ethyl 2,3-dioxobutanoate (V) was first prepared by Bouveault (2). In 1903 Bouveault and Wahl (3) oxidized malonic ester to diethyl mesoxalate (VI). Wahl (19) prepared 3-phenyl-2,3-dioxopropanoate (VII) initially in 1907.

Table 1. Representative tricarbonyl compounds.



Methods employed in the preparation of tricarbonyl compounds include the direct oxidation of  $\beta$ -diketones with nitrogen trioxide or selenium dioxide. A second method involves the treatment of a  $\beta$ -diketone alternately with liquid bromine and potassium acetate and subsequent removal of a molecule of acetyl bromide by heating. Active methylene compounds have also been

condensed with nitroso compounds and the intermediates hydrolyzed to the corresponding tricarbonyl compounds. The preparations yield, in general, the hydrates of the desired tricarbonyl compound from which the pure, yellow or orange anhydrous compound may be obtained by vacuum distillation.

Calvin and Wood (14) compared the absorption spectra of biacetyl and triketopentane (III) and postulated that the tricarbonyl compound was a non-coplanar molecule. The absorption spectra of biacetyl and triketopentane, taken in pure paraffin hydrocarbon solvents, differed but little with slight shifts toward the red on addition of the third carbonyl group. This similarity in spectra was taken as evidence that the electronic excited state involved oscillation between only two carbonyl groups at a time. A coplanar form is said to be possible but the van der Waals repulsions of two carbonyl oxygen atoms render this form less stable than the form in which one acetyl group is not planar with the balance of the molecule.

Tricarbonyl compounds readily form hydrates when exposed to water or moist air. These hydrates are assumed to be formed by the addition of the elements of water to the middle carbonyl group. They react with phenylhydrazine and its derivatives to give phenylhydrazones, with aniline to give anilides and with hydroxylamine to give oximes. In most cases they react with o-phenylenediamine to form quinoxalines. This is a specific reaction for compounds containing at least two adjoining carbonyl groups.

Sachs and Herold (14) and Sachs and Wolff (16) reported base-catalyzed condensations of methyl o-anisyl triketone with p-nitrobenzyl cyanide, acetylacetone, and ethyl malonate. In reporting these compounds, these workers based the postulated structures purely on analytical results and the assumption that the linkage occurred at the middle carbonyl group. No independent proof of structure was made. With other active methylene compounds a reddening of the reaction mixture was taken as evidence that a condensation had been effected.

Hoffman (6) successfully condensed malonic acid with 1,3-diphenylpropanetrione-1,2,3 in the presence of piperidine and pyridine under modified Doebner (5) reaction conditions. Additional evidence is required in order to prove the structures postulated for this product and for the product obtained by the successful condensation of p-nitrophenylacetonitrile with 1,3-diphenylpropanetrione-1,2,3.

Since little evidence has been presented which would provide a rigorous proof of the structure of products obtained from the condensation of active methylene compounds with tricarbonyl compounds, it was believed that synthesis of such compounds through Doebner-Knoevenagel type condensations and proofs of their structures would increase the general knowledge concerning these vicinal tricarbonyl compounds.

## EXPERIMENTAL\*

### Materials Used

The following list indicates the source of the materials which were used in rather large quantities during this study for either preparation or purification of the compounds studied: ethyl benzoylacetate (Eastman 2731); nitrogen dioxide (Matheson Co.); p-nitrophenylacetonitrile (Eastman 1115); methyl iodide (Eastman 164); malonic acid (Eastman 695); n-butyl ether (Eastman 173); cyclohexane (Eastman 702); pyridine (General Chemical Co. 2165); and piperidine (Eastman P687). Only pyridine and piperidine required repurification. Both were dried and distilled before use.

### Equipment

Special equipment used in this study consisted of an active hydrogen analytical apparatus fabricated according to the diagram given by Siggia (18), a Fisher Titrimeter, a Fisher Densitometer, a low temperature condenser, and a one liter, three necked flask with a sintered glass disc and gas inlet sealed in the bottom.

### Preparation of Starting Materials

Ethyl 3-Phenyl-2,3-dioxopropanoate. A total of 85 gm of

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\*All melting points and boiling points were corrected for emergent stem.

this substance was prepared at the beginning of this study. A typical preparation was executed as follows.

Liquid nitrogen dioxide was prepared by condensing gaseous nitrogen dioxide as it was allowed to escape from a high pressure cylinder. Condensation was effected by passing the vapors through a low temperature condenser cooled by a mixture of ice and salt.

Ethyl benzoylacetate (100 gm), acetic anhydride (30 gm) and dry ether (200 ml) were placed in a one liter, three necked flask with a sintered glass disc and gas inlet in the bottom. A thermometer, a mechanical stirrer, and a water condenser equipped with a calcium chloride filled drying tube and a gas washer were placed in the three necks of the flask. The flask was cooled by immersion in an ice-water bath.

The vapors of liquid nitrogen dioxide (92 gm) were bubbled through the stirred reaction mixture over a period of three hours. The vapors were forced under light pressure of dried nitrogen gas, through a sight flask and subsequently into the reaction vessel through the sintered glass disc. The rate of addition of the vapors was regulated by heating or cooling the liquid nitrogen dioxide so that nearly one hundred percent of the vapors were absorbed by the solution.

The temperature of the mixture was maintained at 3-5° C. throughout the reaction. When the addition of the nitrogen dioxide was complete, the ice bath and flask were allowed to warm slowly to room temperature and to stand at room temperature overnight.

The ethereal solution was transferred to a separatory funnel and washed with ten 50 ml portions of a one to one mixture of 20 percent potassium carbonate-saturated sodium chloride solution followed by ten 50 ml portions of saturated sodium chloride solution. The ether and remaining water were removed by distillation at reduced pressure. The residue was distilled under reduced pressure and a crude fraction with a b. p. of 90-190° C. was collected. The crude fractions from five preparations (174.3 gm) were combined and fractionated at reduced pressure through a twenty-four inch fractionating column packed with glass helices. The fraction boiling at 86-89° C. at 0.2 mm was collected and had the following physical constants:  $n_D^{20}$  1.5141;  $d_4^{20}$  1.187. The values listed in the literature for these constants were b. p. 150-153° C. at 13.0 mm (19),  $n_D^{20}$  1.5191 (17), and  $d_4^{20}$  1.188 (19). The 85 gm of product represented a 15.9 percent yield, based on the total quantity of ethyl benzoylacetate used.

#### Condensation Reactions of Ethyl 3-Phenyl-2,3-dioxopropanoate

Condensation of Ethyl 3-Phenyl-2,3-dioxopropanoate with Malonic Acid. All condensations attempted in this study were of the Knoevenagel (9) or Doebner(5) type.

A typical procedure used for the condensation of malonic acid with ethyl 3-phenyl-2,3-dioxopropanoate was as follows.

A 3 gm sample of ethyl 3-phenyl-2,3-dioxopropanoate, 1.514 gm of malonic acid and 4.39 gm of pyridine were placed in a clean dry 50 ml Erlenmeyer flask and the mixture was stirred at room

temperature until solution of the solid was complete. To this solution was added 0.1 gm of piperidine and the mixture was heated on a water bath for three hours.

The solution turned deep red and a gas, later proven to be carbon dioxide, was evolved during the early part of the reaction. Attempts were made to determine quantitatively the amount of carbon dioxide evolved during the reaction by sweeping the carbon dioxide with dry nitrogen into a tared drying tube filled with Ascarite.

The red solution was poured into a beaker containing concentrated hydrochloric acid (20 ml) and cracked ice (60 gm) and the mixture was stirred mechanically until all of the ice had melted. The acid solution was extracted with five 20 ml portions of ether. The ether was removed at room temperature under an air stream and the residue was dissolved in 5 percent sodium carbonate solution. The alkaline solution was extracted with 50 ml of ether and the extract discarded. The aqueous alkaline solution was acidified to pH2 (Congo Red paper) and was extracted with ether. The solvent was then evaporated to give an acidic residue. This residue was subsequently extracted with small portions of hot cyclohexane. Upon cooling, the cyclohexane solution deposited white crystals which were recrystallized from chloroform and petroleum ether. The product was a white crystalline solid, 1.57 gm with a m. p. 101-102° C. This represented a 40.5 percent yield based on a calculated molecular weight of 266 for the product. Table 2 summarizes conditions employed and the yields obtained.

Table 2. A summary of attempted condensation reactions involving ethyl 3-phenyl-2,3-dioxopropanoate and malonic acid.

| Tricar-<br>bonyl<br>compd. : | Malonic<br>Acid<br>: | Pyri-<br>dine<br>: | Piper-<br>idine<br>: | Heating<br>time<br>: | Crude<br>acid<br>: | Product<br>: | Yield <sup>1</sup><br>per-<br>cent |
|------------------------------|----------------------|--------------------|----------------------|----------------------|--------------------|--------------|------------------------------------|
| :                            | (gm)                 | :                  | :                    | (hrs)                | :                  | (gm)         | :                                  |
| 3.00                         | 1.514                | 4.39               | 1.85                 | 6                    | 3.26               | 1.53         | 40.0                               |
| 2.00                         | 1.010                | 2.89               | 1.21                 | *                    | 2.74               | 0.10         | 2.7                                |
| 3.00                         | 1.514                | 4.39               | 0.10                 | 3                    | 2.93               | 1.57         | 40.5                               |
| 3.00                         | 1.514                | -                  | 0.10                 | 3                    | 2.50               | 0.00         | 0.0                                |
| 3.00                         | 1.514                | 4.39               | -                    | 3                    | 2.72               | 1.05         | 27.5                               |

<sup>1</sup> Based upon a calculated molecular weight of 266 for the condensation product.

\* Mixture stood at room temperature for seven days.

Condensation of Ethyl 3-Phenyl-2,3-dioxopropanoate with p-Nitrophenylacetonitrile. A typical condensation of the Knoevenagel (9) type between ethyl 3-phenyl-2,3-dioxopropanoate and p-nitrophenylacetonitrile was effected as follows.

The tricarboxyl compound (3.0 gm) and p-nitrophenylacetonitrile (2.34 gm) were placed in a clean, dry 25 ml Erlenmeyer flask and five drops of piperidine were added. The mixture was heated for five minutes on the water bath and the solution became a thick red brown syrup which hardened to a solid mass on cooling. The amorphous mass was dissolved, with heating, in benzene. The benzene solution deposited light green tinted crystals on cooling which, upon recrystallization from benzene, gave white crystals (0.9 gm) with a m. p. 179-180° C. These crystals

represented a 17 percent yield based on the calculated molecular weight of 368 for the product.

Structure Studies of the Condensation Product of  
Ethyl 3-Phenyl-2,3-dioxopropanoate and Malonic Acid

Carbon-Hydrogen Analysis. The following percentages were obtained from carbon-hydrogen combustion micro analysis of the acid product. Calculated values for a compound  $C_{14}H_{14}O_8$  which could be formed by the condensation of the tricarbonyl compound and malonic acid in a one to one ratio without loss of water are carbon 54.19 percent and hydrogen 4.54 percent. Calculated values for a compound  $C_{13}H_{14}O_6$  which could be obtained from the condensation of the tricarbonyl compound and malonic acid with loss of carbon dioxide are carbon 58.64 percent and hydrogen 5.31 percent. The analysis showed 58.54 percent carbon and 5.25 percent hydrogen to be present.

Neutral Equivalent. The acid product was cleaved rather readily by aqueous sodium hydroxide even in the cold. This cleavage caused the phenolphthalein end point of the titration to fade and inconsistent results were obtained.

Saponification Equivalent. Purified acid product (0.1146 gm) was dissolved in 15 ml of 0.1521 N sodium hydroxide and allowed to stand at room temperature for twelve hours. Back titration required 9.85 ml of 0.1004 N sulfuric acid.

$$\text{Sap. Eq.} = (0.1146 \times 1000) / [15(0.1521) - 9.85(0.1004)] = 88.6$$

A second sample of the acid product (0.0992 gm) was dissolved in 5 ml of 0.3581 N sodium hydroxide and the resulting

solution was heated for two hours at reflux temperature. Back titration required 6.89 ml of 0.0968 N sulfuric acid.

$$\text{Sap. Eq.} = (0.0992 \times 1000) / [5(0.3581) - 6.89(0.0968)] = 88.2$$

Active Hydrogen Determination. Active hydrogen content of the acid product was determined by the Zerewitinoff method as described by Siggia (18).

A 0.2676 gm sample of the purified acid was placed in the reaction flask of the active hydrogen apparatus containing 10 ml of xylene and a glass enclosed iron stirring rod. The system was purged of air with dry nitrogen and closed to the atmosphere. Methyl magnesium iodide (12.8 ml, 0.4711 M) in di-n-butyl ether was added by means of a hypodermic syringe. The reaction vessel was heated in a boiling water bath for fifteen minutes and then was stirred until the gas volume became constant. The stirring was accomplished by rotating the glass enclosed iron plug by means of a magnetic stirring device. The total displacement caused by additions and the gas evolved was 75.2 ml. A blank determination was run on 10 ml of the xylene and it was found that 8.4 ml of methane were evolved. The number of gm of active hydrogen per mole was then calculated as shown.

$$75.2 - 12.8 - 8.4 = 54.0 \text{ ml methane evolved at } 26^{\circ} \text{ C.}$$

$$\frac{54.0 \times 273 \times 266}{299 \times 22,400 \times 0.2676} = 2.19 \text{ gm active H/mole}$$

Distilled water (2 ml) was added to the reaction flask and a total volume change of 10.4 ml was observed. The methane evolved due to the unreacted Grignard reagent was therefore 8.4 ml. The total amount of gas evolved during the complete

experiment was then

$$54.0 + 8.4 + 8.4 = 70.8 \text{ ml at } 26^{\circ} \text{ C.} = 64.9 \text{ ml at } 0^{\circ} \text{ C.}$$

$$266.2/0.2676 \left[ (12.8 \times 4.711 \times 10^{-4}) - (64.9/22,400) \right] = 3.1$$

The last calculation indicates the number of moles of Grignard reagent which added to each mole of the acid product.

A second sample of acid product (0.1281 gm) was dissolved in 5 ml of xylene in the active hydrogen apparatus and treated with 6.4 ml of 0.4711 M methyl magnesium iodide in di-n-butyl ether. A total volume change of 35.4 ml was observed.

$$35.4 - 6.4 - 4.2 = 24.8 \text{ ml methane evolved.}$$

$$\frac{24.8 \times 273 \times 266.2}{299 \times 22,400 \times 0.1281} = 2.10 \text{ gm active H/mole}$$

Carbonyl Group Determination. A carbonyl determination was made on the acid by the method described by Siggia (18). The acid (0.134 gm) was placed in a 250 ml Erlenmeyer flask and 30 ml of hydroxylamine hydrochloride in ethanol and 100 ml of bromphenol blue indicator in pyridine-alcohol solution were added. The solution was heated one and a half hours on a water bath and allowed to stand overnight. The mixture required 2.02 ml of 0.5041 N alcoholic sodium hydroxide to reach the end point. It was calculated that exactly 1.00 ml of the alkali was needed to neutralize the acid groups of the compound therefore 1.02 ml of base was required to neutralize the liberated HCl. The carbonyl group was calculated as the percent of the sample that contained one ketone or aldehyde carbonyl group.

$$\frac{1.02 \times 0.5041 \times 266.2 \times 100}{0.134 \times 1000} = 102.1 \text{ percent carbonyl}$$

Calculated as a "carbonyl equivalent" the data shows the equivalent weight to be 261.

$$(0.134 \times 1000)/(1.02 \times 0.5041) = 261$$

This represents one carbonyl group per molecule.

Identification of Fragments from Saponification of Acid Product. A 1.781 gm sample of the acid condensation product was added to excess sodium hydroxide. The mixture was heated at reflux temperature for three hours. The solution was made just acid to litmus paper and extracted with five 20 ml portions of ether. The ether was removed by passing a stream of air over the solution and a crystalline solid (0.0985 gm) with a m. p. of 121-123° C. was recovered. The melting point of this solid mixed with authentic benzoic acid was 119-121° C. The solution was acidified further to pH 2 (Congo Red paper) and was extracted with ether. The ether was removed and a white crystalline solid (0.731 gm) with a m. p. of 121-123° C. was obtained. A mixed melting point with authentic benzoic acid was 122-124° C. The total of 0.829 gm crude benzoic acid recovered represents 101 percent of that expected from the sample saponified.

A one ml portion of the aqueous acid solution was exactly neutralized with aqueous sodium hydroxide with coincident dilution to two and one half ml and subjected to the following tests which Huntress and Mulliken (7) describe as being specific for malic acid. Ammonium chloride and calcium chloride were added to one portion. Boiling produced no precipitate but upon addition of three volumes of alcohol, a white precipitate formed. To a

second portion of the neutral solution was added a solution of lead acetate. A voluminous white precipitate formed immediately. To a third portion two drops of a 5 percent ferric chloride solution were added. A deepening of the yellow color was observed immediately. The iodoform test gave inconclusive results.

Conversion of the acid fragment to fumaric acid was effected by the method described by Huntress and Mulliken (7). A 50 ml portion of the acid solution was made alkaline and a large excess of solid sodium hydroxide was added. The solution was evaporated to dryness and the residue was baked for three hours at  $130^{\circ}\text{C}$ . in an electric oven. The resulting white solid was acidified strongly with concentrated sulfuric acid and filtered. The precipitate was extracted with ethyl alcohol and the extract was evaporated to dryness under an air stream. A white solid (0.5605 gm) was recovered and was sublimed under reduced pressure. The white sublimate had a m. p.  $284-286^{\circ}\text{C}$ . in a sealed tube. Michael (11) reports a melting point of  $286-287^{\circ}\text{C}$ . for fumaric acid.

A sample of authentic fumaric acid was prepared by dissolving maleic anhydride in an excess of aqueous sodium hydroxide and evaporating the solution to dryness. The white solid residue was baked for three hours in an electric oven at  $130^{\circ}\text{C}$ . The solid was acidified strongly with concentrated sulfuric acid and the solution was filtered. The precipitate was extracted with ethyl alcohol and the alcohol was evaporated under an air stream. The resultant solid was sublimed under reduced pressure and the sublimate had a m. p. of  $283-285^{\circ}\text{C}$ . in a sealed tube. A mixture of

authentic fumaric acid and the sublimate from the saponification had a m. p. of  $284-286^{\circ}$  C. in a sealed tube.

Structure Studies of the Condensation Product  
of Ethyl 3-Phenyl-2,3-dioxopropanoate and  
p-Nitrophenylacetonitrile

Carbon-Hydrogen Analysis. The following results were obtained from carbon-hydrogen combustion micro-analysis of the condensation product. Calculated values for the compound  $C_{19}H_{16}O_6N_2$  which could be formed by the one to one addition of the tricarbonyl compound and p-nitrophenylacetonitrile are carbon 61.95 percent and hydrogen 4.38 percent. The analysis showed 61.93 percent carbon and 4.26 percent hydrogen to be present.

Saponification Equivalent. A 0.0834 gm sample of the condensation product was added to 15 ml of 0.1521 N sodium hydroxide and was heated for two hours. The solution turned a very deep red color during the saponification. The solution was titrated with a Fisher Titrimeter. The pH was plotted against ml of acid added and it was found that 18.10 ml of 0.1004 N sulfuric acid was required to reach the end point.

$$\text{Sap. Eq.} = \frac{0.0834 \times 1000}{(15.00 \times 0.1521) - (18.10 \times 0.1004)} = 179.7$$

A second sample (0.0731 gm) was saponified in 15 ml of 0.1521 N sodium hydroxide. The resultant solution was titrated with standard acid using the Titrimeter and the results were plotted as before. The end point was reached after the addition of 18.50 ml of 0.1004 N sulfuric acid.

$$\text{Sap. Eq.} = \frac{0.0731 \times 1000}{(15.00 \times 0.1521) - (18.50 \times 0.1004)} = 172.1$$

Active Hydrogen Determination. A 0.1919 gm sample of the condensation product was placed in the reaction vessel of the apparatus and freshly distilled xylene (10 ml), b. p. 137-138° C., was added. The system was purged of air and closed to the atmosphere. Methyl magnesium iodide (6 ml, 0.4711 M) in di-n-butyl ether was added and the solution was heated for fifteen minutes in a boiling water bath and then stirred magnetically until the volume of the gas became constant. The total displacement caused by additions of liquid and the evolution of gas was 18.65 ml.

18.65 - 6.0 = 12.65 ml methane evolved.

$$\frac{12.65 \times 273 \times 368.3}{300 \times 22,400 \times 0.1919} = 0.99 \text{ gm active H/mole}$$

Carbonyl Group Determination. A carbonyl determination was made with 0.2613 gm of condensation product. The sample, hydroxylamine hydrochloride solution (30 ml) and bromphenol blue indicator solution (100 ml) were heated for one hour and allowed to stand at room temperature for twenty-four hours. Titration with 0.5041 N alcoholic sodium hydroxide required 1.40 ml to reach the end point.

$$\frac{1.40 \times 0.5041 \times 368.3 \times 100}{0.2613 \times 1000} = 99.7 \text{ percent carbonyl}$$

Calculated as a "carbonyl equivalent", the equivalent weight was found to be 371.

$$(0.2613 \times 1000)/(1.40 \times 0.5041) = 371$$

These results represent one carbonyl group per molecule.

Identification of the Fragments of Saponification. A sample (0.874 gm) of the condensation product was heated for two hours with 25 ml of 0.4723 N sodium hydroxide. During the saponification a very strong odor of ammonia was noticed. The alkaline solution was made just acid to litmus paper and was extracted with ether. Only a slight trace of colored material remained after evaporation of this extract. The solution then was acidified to pH 2 (Congo Red paper) and was extracted with ether. A dark red residue (0.92 gm) remained after evaporation of the etheral solution. The residue was dissolved in alkali and the solution was acidified. A solid yellow precipitate formed and was filtered from the solution and washed with water. The yellow solid (0.90 gm) melted with the evolution of gas at 233-235° C.

The product was dried and 0.0958 gm was dissolved in 8.00 ml of 0.1521 N sodium hydroxide and was allowed to stand overnight. Back titration with standard acid using the Titrimeter required 6.80 ml of 0.1004 N sulfuric acid to reach the end point.

$$N. E. = \frac{0.0958 \times 1000}{(8.00 \times 0.1521) - (6.8 \times 0.1004)} = 177.7$$

Active Hydrogen Determination. A 0.1744 gm sample of acid material from the saponification and 5.0 ml of xylene were placed in the reaction flask. The system was purged with dry nitrogen and then closed. Methyl magnesium iodide (6.0 ml, 0.4711 M) in di-n-butyl ether was added and the reaction vessel was heated for fifteen minutes. The mixture was stirred magnetically until the gas volume became constant. The total volume change was 45.0 ml.

$45.0 - 4.2 - 6.0 = 34.8$  ml methane evolved

$$\frac{34.8 \times 273 \times 360}{305 \times 22,400 \times 0.1744} = 2.87 \text{ gm active H/mole}$$

To determine the quantity of the Grignard reagent that had added to the compound, 2.0 ml of water were added and the total volume change was observed to be 21.8 ml. Of this 19.8 ml was due to the methane evolved. The total amount of gas evolved during the reaction was then

$$34.8 + 4.2 + 19.8 = 58.8 \text{ ml at } 32^{\circ} \text{ C} = 52.6 \text{ ml at } 0^{\circ} \text{ C.}$$

The moles of Grignard adding per mole of compound was found to be

$$(360/0.1744) [(6.0 \times 4.711 \times 10^{-4}) - (52.6/22,400)] = 0.99$$

Carbon-Hydrogen Analysis. The following results were obtained from carbon-hydrogen combustion micro analysis of the acid product from the saponification. Calculated values for the compound  $\text{C}_{17}\text{H}_{13}\text{O}_8\text{N}$  are carbon 56.83 percent and hydrogen 4.59 percent. Analysis showed 56.77 percent carbon and 4.55 percent hydrogen to be present.

Decarboxylation of Acid. An attempt was made to decarboxylate the acid by the method reported by Johnson et al. (8). A 0.31 gm sample of the acid, 2 ml of quinoline, and 0.4 gm of copper powder were heated together for five minutes. The resulting red solution was poured into hydrochloric acid solution and a brown precipitate which melted at  $107\text{--}109^{\circ} \text{ C.}$  precipitated immediately. This precipitate could not be recrystallized and was therefore not identified.

## Sample Calculations

General formulas used in calculation of the results are given below with the calculation to which they apply.

Saponification Equivalent.

$$\text{Sap. Eq.} = (A \times 1000) / [(B \times C) - (D \times E)]$$

A = weight of sample

B = volume of standard base used

C = normality of base

D = volume of standard acid used

E = normality of standard acid

Active Hydrogen Determination.

$$A - B - C = D$$

$$\frac{D \times 273 \times E}{(T + 273) \times 22,400 \times F} = \text{gm active H/mole}$$

A = total volume of gas evolved

B = volume of Grignard reagent added

C = blank on solvent

D = gas evolved due to active hydrogen

E = molecular weight of compound

F = weight of sample

T = temperature of gas, degrees Centigrade

Carbonyl Determination.

$$(A/B) [(C \times D) - (E/22,400)]$$

A = molecular weight of carbonyl compound

B = weight of sample

C = ml Grignard reagent added

D = moles Grignard per ml reagent

E = total volume of gas evolved at 0° C.

Carbonyl Equivalent.

$$(A \times 1000)/(B \times C)$$

A = weight of sample

B = volume of standard base used

C = normality of base

Neutralization Equivalent.

$$(A \times 1000)/[(B \times C) - (D \times E)]$$

A = weight of sample

B = volume of standard base used

C = normality of base

D = volume of standard acid used

E = normality of acid

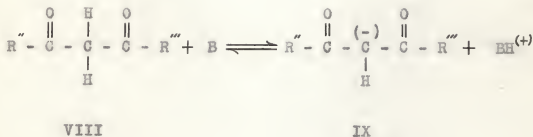
DISCUSSION AND CONCLUSIONS

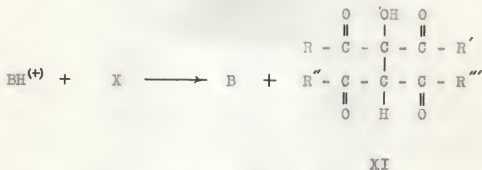
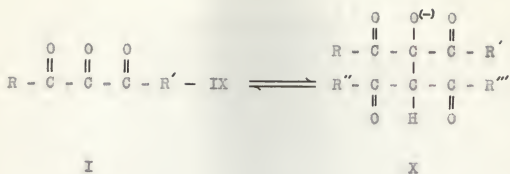
A critical point in the preparation of ethyl 3-phenyl-2,3-dioxopropanoate was apparently the rate of decomposition of the intermediate solid formed in the reaction mixture during the oxidation of ethyl benzoylacetate with nitrogen dioxide. More rapid decomposition of the solid resulted in an immediate temperature increase and the evolution of large quantities of nitrogen dioxide. Addition of water to the mixture containing the solid intermediate resulted in violent decomposition. Rapid decomposition of this intermediate invariably resulted in decreased yields of the desired product.

Distillation of the crude ethyl 3-phenyl-2,3-dioxopropanoate always resulted in the condensation of varying amounts of solid benzoic acid in the condenser. This acid was removed by washing an ethereal solution of the first distillate with sodium carbonate-saturated sodium chloride solution. Benzoic acid never appeared during redistillation of this washed product. The saturated sodium chloride solution was employed to remove as much of the residual moisture as possible from the liquid.

The physical properties of the pure ethyl 3-phenyl-2,3-dioxopropanoate agreed well with those reported for this compound by Wahl (19) and Sharp (17). The p-nitrophenylhydrazone derivative of the tricarbonyl compound and the hydrate both exhibited the same melting point respectively as those reported by Sharp (17).

Theoretically, condensations between tricarbonyl compounds and active methylene compounds are base-catalyzed reactions which proceed according to the following sequence of reactions.





The negatively charged particle (IX) formed by the action of the base on the active methylene compound (VIII) could react with the tricarbonyl compound (I) and the anion (X) in turn could react with the conjugate acid of the base (BH) to regenerate the base and complete the condensation. If the reaction proceeds in this manner, the acid strength of I would be an important factor controlling the reaction. Theoretically any one of the three carbonyl groups could act as shown. Logically, that carbonyl group which is coupled the least by resonance with the remainder of the molecule would be the one whereon condensation should occur.

Other factors to be considered in condensations of this type were the steric influences and possible rearrangements. The size of the terminal groups of the tricarbonyl compound as well as the dimensions of the groups present in the condensing active

methylene compound would tend to retard condensation at the adjacent carbonyls more than at the central carbonyl group. The terminal groups of ethyl 3-phenyl-2,3-dioxopropanoate, being relatively large in size, could be expected to produce pronounced steric effects.

Malonic acid was chosen as an active methylene compound to be condensed with ethyl 3-phenyl-2,3-dioxopropanoate due to the relatively small size of the molecule and the anticipated ease with which the expected crystalline products could be manipulated. The inclusion of the acid function in the condensed molecule also would contribute greatly to the determination of the molecular weight of the compound.

The conditions employed to effect the condensation between ethyl 3-phenyl-2,3-dioxopropanoate and malonic acid were an outgrowth of the work of Knoevenagel (9) and Doebner (5). Pyridine was used as a solvent and piperidine as a catalyst in the condensations involving malonic acid and the modifications developed by Hoffman (6) in condensing diphenyltriketone and malonic acid were employed.

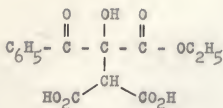
The conditions for the condensation apparently were not too critical as nearly identical yields of pure product were obtained whether large quantities of piperidine and long periods of heating or small quantities of piperidine with shorter heating periods were used. No condensation product was obtained from any reaction regardless of conditions, until after evolution of carbon dioxide had taken place. This evolution usually began within ten minutes

after the mixture was first heated and continued for about one hour thereafter.

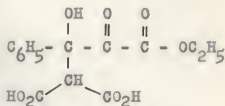
Quantitative determinations were made of the amount of carbon dioxide evolved in an attempt to determine if sufficient gas was produced to render impossible the existence of a condensation product formed by the simple addition of malonic acid to the tricarbonyl compound with or without rearrangement. These determinations were inconclusive in all cases.

Difficulty was experienced in finding a solvent which would permit the separation of the acid product from the red sticky gum that always accompanied its production. All of the commonly used solvents readily dissolved both the desired product and the gum except cyclohexane which proved to be capable of selectively extracting the condensation product from the crude acid product with only a minimum of the red impurity. The acid product was obtained by extracting the crude acid with small portions of hot cyclohexane. The white solid which precipitated after the solvent had cooled was removed by filtration. Following the first extraction, the product crystallized readily from chloroform on the addition of petroleum ether. Samples for carbon-hydrogen analysis were recrystallized from ethyl acetate.

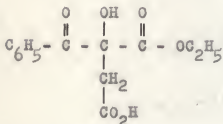
Assuming that addition or condensation did occur, the formulas XII, XIII, XIV, and XV shown below were the most logical possibilities for the structure of the product. Formulas XII and XIII represent simple addition of the two reactants and formulas XIV and XV represent addition with loss of carbon dioxide.



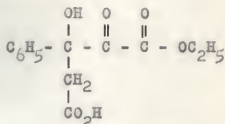
XII



XIII



XIV



XV

In addition each of these structures could have an unsaturated counterpart due to loss of a molecule of water. It would seem reasonable, however, that such olefinic molecules would be colored due to their similarities to the tricarbonyl compounds and since the product was white the olefinic structures are not included at this time.

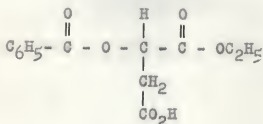
Saponification equivalents of the pure acid product averaged 88.4 for samples which were saponified either at room or at reflux temperature. This value indicated that the molecular weight of the acid was some approximate multiple of 89. This indicated that the condensation product was not one of the substituted malonic acids, XII or XIII, which would be expected from a simple addition of malonic acid to the tricarbonyl compound. The calculated saponification equivalent of XII and XIII was 77.5 and

for XIV and XV it was 88.7.

The products of saponification were found to be benzoic acid (in theoretical amount based on formula XIV and the weight of sample) and malic acid which are equivalent to three acid groups per molecule.

Carbon-hydrogen analysis gave results in agreement with the molecular formula  $C_{13}H_{14}O_6$  which further eliminated XII and XIII as possibilities. This result coupled with saponification data indicated that the product was a mono-basic acid.

If rearrangement had occurred during the condensation an additional structure which may be a possibility is written as follows.



#### XVI

This is similar in gross structure to the rearranged product reported by Kohler and Erickson (10) which arose from the one to one reaction of 1,3-diphenylpropanetrione-1,2,3 and phenyl magnesium halide.

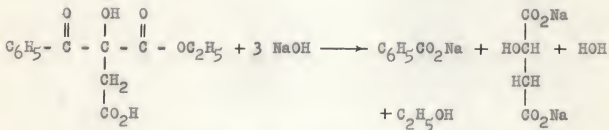
Active hydrogen determinations according to the procedure of Sigga (18) indicated that two hydrogen atoms not attached to carbon were present in the molecule. This eliminated structure XVI which has but one active hydrogen. Furthermore, three moles of Grignard were added for each mole of product present which

further eliminates XVI, which structure should take up four moles of Grignard. These data conform to structures XIV and XV, both of which have two active hydrogens per molecule and would add three moles of Grignard per molecule.

Carbonyl determinations according to the procedure of Siggia (18) showed one carbonyl group to be present in the condensed molecule, which again supported structures XIV and XV.

Fragments identified from the saponification of the acid product were benzoic acid and malic acid. The latter was identified tentatively by qualitative tests and positively by its conversion to fumaric acid. These tests were described by Huntress and Mulliken (7).

Logically only structure XIV could give rise to benzoic acid and malic acid assuming that a gross rearrangement of XV did not occur upon saponification. The amount of benzoic acid recovered was 100 percent of theory which renders the rearrangement of XV highly improbable. The saponification of XIV apparently proceeds as follows.

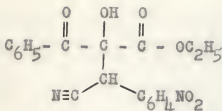


The cumulative data conclusively supports formula XIV as representing the actual structure of this condensation product. It is quite evident that the central carbonyl group in this case was the most reactive.

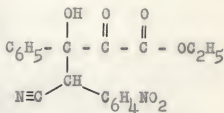
The condensation of p-nitrophenylacetonitrile with ethyl 3-phenyl-2,3-dioxopropanoate was easily effected through a Knoevenagel (9) type reaction. Addition of piperidine to the mixture of p-nitrophenylacetonitrile and ethyl 3-phenyl-2,3-dioxopropanoate produced an immediate reaction with the evolution of heat and formation of a red color. The reaction was attempted using benzene as a solvent and the piperidine was added only after the solution of the reactants in the benzene was complete. Smaller yields were realized with the latter method and so it was abandoned as a preparative method. Although the reaction was exothermic, heating the mixture produced higher yields of the desired product.

The product was easily purified by recrystallization from benzene. The warm solvent readily dissolved the red sticky mass, which was formed along with the desired product, and the latter crystallized from the benzene solution when it was cooled. Samples were purified for carbon-hydrogen analysis by repeated recrystallizations from benzene. The product so obtained possessed a very slight green tint and was light and fluffy.

Assuming a one to one addition of the reactants with no rearrangement occurring, the formulas XVII and XVIII could logically be proposed as possibilities for the structure of the product.



XVII



XVIII

These structures could also have unsaturated counterparts due to loss of a molecule of water. The product obtained was nearly colorless and since the unsaturated molecules would closely resemble the parent tricarbonyl compound, it was logical to assume that unsaturated products should exhibit color. The olefinic products will not be considered here.

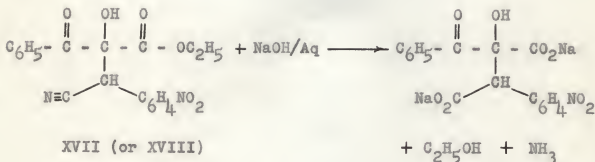
Saponification equivalents of the pure product gave an average value of 176. These data indicate that the molecular weight of the compound is some approximate multiple of 176 which supports either XVII or XVIII as a possible structure. These data are not deemed too reliable due to the inherent inaccuracy of selecting the end point of the potentiometric titration.

The odor of ammonia which appeared in some quantity during the saponification of the product was indicative of the presence of the nitrile group in the condensed molecule. The presence of this group and the ethoxyl group accounts for the two saponifiable groups in each molecule.

Carbon-hydrogen analysis gave results agreeing with a molecular formula  $\text{C}_{19}\text{H}_{16}\text{O}_6\text{N}_2$ . Active hydrogen analysis indicated that one active hydrogen atom was present per molecule and carbonyl determinations showed that one carbonyl group was present

in each molecule. Both of these results verified formula XVII or XVIII for the condensation product.

The dibasic acid obtained from saponification of the product gave a neutralization equivalent of 177.7 and a carbon-hydrogen analysis corresponded to a molecular formula  $C_{17}H_{13}O_8N$ . The amount of this acid recovered is sufficient to eliminate the possibility of the molecule undergoing carbon-carbon cleavage. No benzoic acid was obtained from the saponification of this molecule. The saponification of the condensation product apparently proceeds according to the following equation assuming XVII to be the molecule saponified.



Either structure XVII or XVIII agrees with all of the evidence presented herein. Had the molecule been cleaved more than once the structure of the saponification products possibly might have been used to determine which carbonyl group had been attacked by the condensing molecule. The data presented indicate that structures XVII and XVIII are equally possible, and further data are necessary in order to determine at which carbonyl group the addition occurred. It seems reasonable, however, that the central carbonyl group was involved, but this inference is based

solely upon analogy to the malonic acid product.

#### SUMMARY

Ethyl 3-phenyl-2,3-dioxopropanoate was found to condense with p-nitrophenylacetonitrile and malonic acid in the presence of organic bases under appropriate reaction conditions.

Evidence was found which supported the formula  $C_{13}H_{14}O_6$  for the condensation product of ethyl 3-phenyl-2,3-dioxopropanoate and malonic acid. Structure proof for the condensed molecule indicated that malonic acid condensed with the tricarbonyl compound at the medial carbonyl group with coincident loss of a molecule of carbon dioxide. Heat and dilute alkali degraded the acid condensation product to benzoic acid, malic acid and ethyl alcohol. Active hydrogen determinations showed that two hydrogen atoms not attached to carbon were present and carbonyl determinations indicated that one carbonyl group was present in the molecule.

A molecular formula  $C_{19}H_{16}O_6N_2$  was found for the condensation product of ethyl 3-phenyl-2,3-dioxopropanoate and p-nitrophenylacetonitrile. Saponification of this product yielded a dibasic acid with a molecular formula  $C_{17}H_{13}O_8N$ , ethyl alcohol, and ammonia. One active hydrogen and one carbonyl group were found to be present in the condensed molecule. The structural evidence obtained thus far does not permit designation of which carbonyl group was involved in the reaction.

## ACKNOWLEDGMENTS

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## LITERATURE CITED

- (1) Abderhalden, E., and H. Schmidt.  
Experiments with triketohydrindene hydrate. *Ztschr. Physiol. Chem.* 85:143-147. 1913. Original not seen.  
Abstract in *Chem. Abs.* 7:3765. 1913.
- (2) Bouveault, L.  
Preparation of 2,3-diketobutyric ester. *Bull. Soc. Chim.* (3)33:475-481. 1903. Original not seen. Abstract in *Jour. Chem. Soc. (London) Abstr.* 11, 1904. p. 588
- (3) Bouveault, L., and A. Wahl.  
Sur les ethers isonitrosomaloniques et leur transformation en ethers mesoxaliques. *Compt. rend.* 137:196-198. 1903.
- (4) Calvin, M., and C. L. Wood.  
Conjugation of carbonyl groups and the absorption spectrum of triketopentane. *Amer. Chem. Soc. Jour.* 62:3152-3155. 1940
- (5) Doebner, O.  
Synthese der sorbinsäure. *Ber. der Deutsch. Chem. Gesell.* 33:2140-2142. 1900.
- (6) Hoffman, H. A.  
The chemistry of vicinal tricarbonyl compounds: Condensation reactions of 1,3-diphenylpropanetrione-1,2,3. Unpublished Ph. D. thesis, Kansas State College, Manhattan, Kansas, 1950.
- (7) Huntress, H., and S. P. Mulliken.  
Identification of pure organic compounds. New York: John Wiley and Sons, 1941.
- (8) Johnson, J. R., A. F. Shepard, and N. R. Winslow.  
The simple halogen derivatives of furan. *Amer. Chem. Soc. Jour.* 52:2083-2091. 1930.
- (9) Knoevenagel, E.  
Condensation von malonsäure mit aromatischen aldehyden durch ammoniak und amine. *Ber. der Deutsch. Chem. Gesell.* 31:2596-2619. 1898.
- (10) Kohler, E. P., and J. L. E. Erickson.  
Cleavage of beta-diketones I. Cleavage by organic magnesium compounds. *Amer. Chem. Soc. Jour.* 53:2301-2309. 1931.

- (11) Michael, A.  
Zur schmelzpunktbestimmung von hochschmelzen und  
sogenannten unschmelzbaren organischen verbindungen.  
Ber. der Deutsch. Chem. Gesell. 28:1629-1633. 1895.
- (12) de Neufville, R., and H. von Peckmann.  
Ueber das diphenyltriketone. Ber. der Deutsch. Chem.  
Gesell. 23:3376-3379. 1890.
- (13) Sachs, F., and H. Barschall.  
Ueber triketone. I. Ber der Deutsch Chem. Gesell.  
34:3047-3052. 1901.
- (14) Sachs, F., and V. Herold.  
Ueber triketone IV. Ber. der Deutsch. Chem. Gesell.  
40:2714-2730. 1907.
- (15) Sachs, F., and A. Rohmer.  
Ueber triketone II. Ber. der Deutsch. Chem. Gesell.  
35:3307-3312. 1902.
- (16) Sachs, F., and W. Wolff.  
Ueber triketone III. Ber. der Deutsch. Chem. Gesell.  
36:3221-3236. 1903.
- (17) Sharp, D. B.  
Mechanisms of the cleavage of certain phenylhydrazones  
by bromine. Amer. Chem. Soc. Jour. 71:1106-1108.  
1949.
- (18) Siggia, S.  
Quantitative organic analysis via functional groups.  
New York: John Wiley and Sons. 1941.
- (19) Wahl, M. A.  
Sur le benzoylglyoxalate d'ethyle. Compt. rend.  
144:211-214. 1907.